Review Article

New pharmacotherapies for diabetic retinopathy

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Abstract: Diabetic retinopathy (DR) is the most common microvascular complication in patients with diabetes mellitus (DM), and remains the single greatest cause of blindness in working age adults around the world. In this article, we review the evolution of pharmacotherapies for both diabetic macular edema (DME) and DR such as anti-vascular endothelial growth factor inhibitors and various steroid formulations, as well as other emerging pharmacotherapies currently in late stage clinical testing for this disease.

Keywords: Diabetic retinopathy (DR); diabetic macular edema (DME); vascular endothelial growth factor; steroids; clinical trials

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Introduction to diabetic retinopathy (DR) and diabetic macula edema pathogenesis

DR is the most common microvascular complication in patients with diabetes mellitus (DM), and remains the single greatest cause of blindness in working age adults around the world (1,2). DR results in vision loss through two main mechanisms: (I) an ischemic retinopathy that results in aberrant retinal neovascularization and fibrovascular proliferation causing vitreous hemorrhage, traction, and ischemia on the retina; and (II) macular edema resulting from breakdown of the blood retina barrier (1). The pathophysiology of DR remains incompletely understood, although several biochemical pathways linking chronic hyperglycemia to microvascular complications have been proposed. Some potential causes include: advanced glycated end-products, oxidative stress, polyol accumulation, and protein kinase C activation (3). Ultimately, hyperglycemia is primarily responsible for the complications of DM, including DR, although there are patients with poorly controlled DM who do not develop DR, and those with well-managed glucose levels without hypertension that will develop DR, suggesting there may be genetic or environmental factors that affect DR progression independent of glycemic control (4,5).

Clinically, DR manifests in microvascular changes in the retina including microaneurysms, exudative deposits, dot blot hemorrhages, venous beading, retinal neovascularization, and fibrovascular proliferation. DR is traditionally graded based on the classification from the Early Treatment of Diabetic Retinopathy Studies (ETDRS) and classified into non-proliferative and proliferative DR based on these microvascular changes in the retina. Current treatments for non-proliferative DR involve intensive glycemic control, while individuals with proliferative DR or high risk non-proliferative characteristics may require local treatments including laser treatment or intravitreal injections (6).

The treatment of DR and macular edema has gone through substantial changes over the years. The initial landmark studies in DR showed that panretinal photocoagulation (PRP) and focal laser can prevent vision loss in DR, and have now evolved to newer pharmacologic therapies such as intravitreal injection of steroids and anti-VEGF antibodies. This article will focus on a review of pharmacologic treatment for DR, with an emphasis on upcoming pharmacologic therapies in the pipeline for DR.

Systemic treatments

Multiple studies have demonstrated the importance of glycemic control in preventing progression of DR. Both the Diabetes Control and Complication Trial (DCCT) as well as the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that intensive glucose control in both type 1 and type 2 diabetic patients reduced the risk of developing retinopathy and slowed progression of retinopathy (7,8).

In addition, systemic pharmacologic therapy for DR has also been investigated. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study examined the effect of the peroxisome proliferator-activated receptor α (PPAR-α) agonist fenofibrate on cardiovascular disease in type 2 DM. Compared to the placebo group, significantly fewer patients receiving fenofibrate required laser treatment for retinopathy (9). A sub-study of the 5-year trial revealed 4.9% of patients on placebo required first laser therapy compared to 3.4% on fenofibrate, and that 200 mg/d of fenofibrate reduced retinopathy progression for those with pre-existing disease (10). Expanding on these findings, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, compared to simvastatin alone, patients also receiving 160 mg/d of fenofibrate in combination had a 40% reduction in the odds of retinopathy progressing over 4 years (11). Based on these results, DR was added as an on-label indication for fenofibrate in Australia. Despite the results seen in FIELD and ACCORD, a 2015 meta-analysis of prospective, randomized controlled trials found that lipid lowering therapy did not significantly reduce the risk in worsening hard exudates or severity of DME (12). Fenofibrate can be associated with nausea and GI upset, and rarely myopathy, and serum creatine and transaminases need to be monitored while patients are on fenofibrate therapy, which may contribute to the lack of widespread adoption of fenofibrate for treatment of DR. Given these clinical trial results, further investigation is warranted.

Another oral therapy that has been investigated for DR is ruboxistaurin, a protein kinase C β inhibitor. Laboratory studies and early clinical studies demonstrated ruboxistaurin could prevent VEGF-induced retinal permeability and affect blood flow in patients with DR (13,14).

The PKC-DR2 study group performed a large 685 patient multicenter randomized 3-year trial that demonstrated that oral ruboxistaurin could prevent vision loss and decreased macular edema in treated patients compared to controls (15). Interestingly, ruboxistaurin was not shown to affect progression of non-proliferative DR to DR, and first manifested its beneficial effect at 18 months, suggesting that long-term treatment with ruboxistaurin would be necessary. Clinical development of ruboxistaurin has been aborted, as the FDA required additional clinical trials prior to approval and the sponsor, Eli Lilly, decided to terminate the project.

Non-pharmacologic therapies

Proliferative DR has been traditionally treated with PRP. This was based on the Diabetic Retinopathy Study (DRS), which demonstrated that photocoagulation significantly reduces visual loss from proliferative DR compared to no treatment (16). Although effective in preventing vision loss, PRP can leave patients with significant peripheral vision loss and decreases in night vision, prompting investigations if pharmacologic therapies may be useful for preventing progression for DR.

In the case of DME, for many years, focal laser photocoagulation had been the standard of care for DME. There are two methods of applying laser photocoagulation in the macula: focal laser photocoagulation, which is used for discrete fluorescein leaks identified by fluorescein angiography (FA), and grid laser photocoagulation, which is used for thickened areas of the retina and/or diffuse areas of fluorescein leakage (6). In the ETDRS study, compared to untreated DME patients, those treated with laser experienced a 50% reduction in moderate vision loss over time (17). While the mechanisms of action for focal photocoagulation are still not entirely understood, it can prevent further deterioration of vision if utilized sufficiently early, but does not typically restore lost vision (5). In both the ETDRS and subsequent studies, relatively few patients with vision loss saw any improvements in their best correct visual acuity (BCVA) (17). Thus although laser photocoagulation became the first truly successful treatment for DR and DME in the 1980's, historically, it was not utilized until vascular lesions were severe enough to warrant laser ablation (18). Clinical trials have subsequently shown anti-VEGF drugs to be superior for first-line therapy compared to laser treatment, and while the use of VEGF inhibitors have slowed DR progression, focal and/or grid laser photocoagulation are still utilized in combination and for those who do not respond to anti-VEGF treatment (19).

In addition, newer focal laser treatments using subthreshold laser energy have been investigated to treat diabetic macular edema (DME). The premise of subthreshold photocoagulation is to use a laser with

reduced duty cycle to selectively target the retinal pigment epithelium, while having minimal effect on the sensory retina and choroid (20). This treatment has not been demonstrated to cause visible damage to the retina. Preliminary studies suggest that subthreshold micropulse laser is as effective as ETDRS laser photocoagulation, with the benefit of increased retinal sensitivity (21). While promising, larger clinical studies still need to be performed to determine safety and efficacy in the context of other available treatment modalities.

Anti-VEGF pharmacologic treatments

The vascular pathology seen in DR and DME, notably neovascularization and breakdown of the blood-retinal barrier, led to the idea that VEGF may play a causative role in ophthalmologic neovascularization. In 2007 and 2009, the RISE and RIDE trials examined two intravitreal doses of the anti-VEGF antibody fragment ranibizumab (Genentech, South San Francisco, CA) in patients with DME. In RISE, 44.8% of patients receiving 0.3 mg and 39.2% of those receiving 0.5 mg gained ≥15 ETDRS letters from baseline after 24 months, compared to 18.1% of the patients receiving sham injections, whereas in RIDE, corresponding patient outcomes were respectively 33.6%, 45.7%, and 12.3% (17). A separate but simultaneous DME trial, RESTORE, examined ranibizumab with and without laser treatment, compared to laser photocoagulation alone. After 12 months, 65.2% of patients receiving ranibizumab and 63.6% receiving ranibizumab and laser gained ≥5 BCVA letters, compared to 33.6% receiving laser alone (22). A 2-year extension study with individualized dosing found that ranibizumab was well-tolerated and maintained BCVA improvement, with progressively decreasing injection frequency (23). Overall, these trials demonstrate the superiority of anti-VEGF treatment compared to focal laser for the treatment of DME.

During the course of these trials with ranibizumab, many physicians were treating DME off-label with the anti-VEGF antibody bevacizumab (Genentech, South San Francisco, CA). A prospective phase-3 trial found that after a year, patients receiving 1.25 mg of intravitreal bevacizumab gained a median of 8 BCVA ETDRS letters, compared to those receiving modified EDTRS laser therapy who lost a median of 0.5 ETDRS letters (24).

A third anti-VEGF antibody has also been investigated for DR, Aflibercept (Regeneron, Tarrytown, NY), which was designed using domains of VEGF receptors 1 and 2 fused to the Fc domain of human immunoglobulin G1, and has a binding affinity 100 times greater than either bevacizumab or ranibizumab (25). Two phase 3 trials, VISTA and VIVID, found that after 52 weeks, patients receiving 2 mg intravitreal aflibercept every 4 weeks or every 8 weeks after 5 initial monthly doses had mean BCVA gains of 12.5 and 10.5 ETDRS letters respectively in the VISTA trial, whereas those in the VIVID trial had mean BCVA gains of 10.5 and 10.7 ETDRS letters respectively, compared to mean BCVA gains of 0.2 and 1.2 ETDRS letters respectively for VISTA and VIVID patients receiving laser photocoagulation (26).

In 2012, the DRCR.net conducted Protocol T, a 660 patient study across 89 clinical sites, and attempted to compare the safety and efficacy of these anti-VEGF drugs for treatment of DME. Treatment with aflibercept, ranibizumab, or bevacizumab all resulted in significant visual gains and there was no significant difference in visual acuity between these treatments. However, in pre-specified subgroup analysis of patients with vision of 20/50 or worse, visual gains were significantly greater with aflibercept compared to ranibizumab or bevacizumab (19). In the 2-year follow up, while there was no statistical difference between aflibercept and ranibizumab, there was still a difference between aflibercept and bevacizumab in the subgroup of patients with vision of 20/50 or worse. Additionally, it was noted that significantly fewer injections were required in the 2nd year for all anti-VEGF injections (10 injections first year *vs.* 5 second year). Overall, Protocol T demonstrated that all three drugs were effective in improving visual acuity in patients with DME, with a significant reduction in injection burden in year 2. For patients with vision of 20/50 or worse, aflibercept may provide superior visual gains in year one, but long-term benefits remain unclear.

While these studies demonstrated that anti-VEGF treatment is clinically superior to laser photocoagulation, the use of anti-VEGF in combination with laser treatment was not as well addressed. To this end, based on the visual improvements from ranibizumab seen in the RISE and RIDE trials, the Diabetic Retinopathy Clinical Research Network (DRCR.net) conducted a 5-year study on prompt versus deferred focal/grid laser treatment in DME patients receiving ranibizumab (27). They found no advantage to beginning laser treatment concurrently with ranibizumab compared to waiting 24 weeks to begin laser photocoagulation, and rather, 58% of patients receiving ranibizumab who deferred laser treatment saw an increase of at least 10 letters, compared to 46% who received

ranibizumab with prompt laser photocoagulation. The authors of the study noted the possibility of prompt laser treatment potentially causing more damage to the retina than deferring laser photocoagulation, but patients who deferred laser treatment may require more injections over 5 years, and thus practical limitations such as access to care and cost of treatment can play a role in choosing an appropriate therapy.

Anti-VEGF for proliferative DR

During the RISE and RIDE Trials, it was seen that not only did DME improve, but also progression of DR was inhibited in patients receiving ranibizumab (28). This led to the DRCR.net Protocol S, which demonstrated that ranibizumab was non-inferior to pan-retinal photocoagulation in preventing vision loss from DR (29). These data resulted in the FDA approval of ranibizumab for treatment of all types of DR. In 2017 a phase 2b trial on aflibercept, the CLARITY study, found aflibercept to be non-inferior to PRP for proliferative DR and resulted in improved outcome at 1-year (30). There is currently an on-going Phase 3 trial (PANORAMA) investigating whether aflibercept can prevent progression of DR.

Steroids

While anti-VEGF neutralizing antibodies have been the primary treatment for DME, it is well recognized that the causes of DME are multi-factorial, and there is a significant inflammatory component to disease. Steroids have long been used to treat DME given their effects on multiple inflammatory pathways. They have been shown to inhibit VEGF, as well as inhibit leukocyte recruitment and stabilize the blood retina barrier (31).

Intravitreal triamcinolone acetonide (IVTA) was the first steroid used to treat DME, and has been shown to be effective in multiple studies (32). The DRCR Protocol I demonstrated that IVTA plus laser had similar efficacy as ranibizumab plus laser at 2 years (33,34). IVTA is available in multiple formulations, including preservative-free, all of which are used off-label for DME. Treatments with triamcinolone formulations generally last 2–4 months, however they have significant side effects including progression of cataracts, and glaucoma (35).

Additional formulations and sustained release steroids have subsequently been developed to reduce frequency of injections. Ozurdex (Allergan, Irvine, CA, USA) is a sustained release biodegradable dexamethasone implant with a proposed duration of 3–6 months. In the MEAD trial, 22% of patients with a 0.7 mg dexamethasone intravitreal implant injected every 6 months, and 18% of those with a 0.35 mg implant had at least a 15 letter gain compared to 12% in the sham group (36). 0.7 mg Ozurdex was subsequently FDA approved for the treatment of DME, and a subgroup study from patients treated in the MEAD trial found that Ozurdex improved BCVA and CRT in patients previously treated with anti-VEGF therapy (37). While there were high rates of cataract formation, only 3 patients in the MEAD trial required incisional glaucoma surgery. However, Ozurdex was injected at most every six months in the trial which is less than the q3 month dosing commonly used in practice.

Iluvien (Alimera, Alpharetta, GA) is a sustained release formulation of fluocinolone acetonide (FA) designed to last 3 years. Iluvien was demonstrated to be effective for DME in the FAME trials, two phase III clinical trials investigating a low dose (0.19 g) or high dose (0.50 mg) FA implant (38). While almost all patients developed cataracts, only 5% in the low dose group and 8% in the high dose group required incisional glaucoma surgery (39). Hence although Iluvien carries the potentially serious risk of increasing IOP, the 0.19 mg dose has been FDA approved for treatment of DME. Additionally, in post hoc analysis of patients in the FAME study, it was found that patients on the FA implant also had decreased progression of DR compared to controls, suggesting that long term steroid use can also prevent progression of DR (38).

Retisert (Bausch and Lomb, Rochester, NY, USA), a surgically inserted sustained release FA implant, has also been studied for DME. A prospective clinical trial found Retisert produced significant improvements in visual acuity compared to grid laser (40). However, nearly all of the patients (91%) required cataract surgery, and 34% of patients required incisional glaucoma surgery. Given this side effect profile, Retisert is not FDA approved for DME, and in conjunction with its very high cost is uncommonly used to treat DME (41).

Emerging pharmacotherapies for DR and DME

Numerous new therapies for DR and DME are under active investigation. In *Tables 1* and *2*, we list selected studies that we found on clinicaltrials.gov in December 2017 using the search terms "diabetic retinopathy" and "diabetic macular edema." This produced 439 and 397 studies, respectively. In

Table 1 Diabetic retinopathy studies, Clinicaltrials.gov, December 2017

Study agent	Route	Mechanism	Sponsor	Status	Results	References (PMID)	Clinicaltrials.gov identifier
Somatostatin *vs.* Brimonidine	Topical	Neuroprotective	BCN Peptides	Phase II/III completed 2015	No		NCT01726075
Qi Ming granula	PO	Traditional Chinese Medicine	Chengdu University	Phase II/III completed 2011	No		NCT00904592
Propranolol	PO	Anti-angiogenic	Univ. of Wisconsin	Phase I completed 2015	No		NCT01535495
Doxycycline	PO	Anti-inflammatory	Penn State Univ.	Phase II completed 2012	No		NCT00917553
Octreotide	IM	Endocrinologic	Novartis	Phase III completed 2005	No		NCT00131144
BI 1467335	PO	Inhibitor of AOC3/ SSAO/VAP-1; anti-inflammatory	Boehringer Ingelheim	Phase II underway 2017	No		NCT03238963
Conbercept (*vs.* PRP)	IVT	anti-VEGF receptor fusion protein	Sun-Yat Sen Univ.	Phase II underway 2017	No	28841827	NCT02911311
AKB-9778	Subcutaneous	Tie-2 activator +/– ranibizumab IVT	Aerpio Therapeutics	Phase II completed 2015	No	TIME-2; 27236272	NCT03197870
Emixustat	PO	RPE65 inhibition	Acucela Inc.	Phase II completed 2017	No		NCT02753400
Danshen dripping pills	PO	Traditional Chinese Medicine	Tasly Pharmaceuticals	Phase III underway 2015	No		NCT02388984
Ruboxistaurin	PO	PKC-beta inhibitor	Chromaderm, Inc.	Phase III completed 2005	Yes	23404115	NCT00604383
PAN-90806	Topical	VEGF tyrosine kinase inhibition	PanOptica	Phase I completed 2016	No		NCT02475109
Tesamorelin (HIV pts)	PO	Growth hormone-releasing factor	Theratechnologies	Phase IV underway 2012	No		NCT01591902
Sulodexide	PO	Anti-angiogenic	Ajou Univ. (S. Korea)	Phase II completed 2011	No	24391440	NCT01295775
Levosulpiride	PO	Dopamine receptor blocker, prolactinogenic	Universidad Nacional Autonoma de Mexico	Phase III underway 2016	No	16043870	NCT03161652
Qideng Mingmu	PO	Chinese Traditional Medicine	Chengdu University	Phase II completed 2013	No		NCT01373476

Table 1 (*continued*)

Table 1 (*continued*)

Study agent	Route	Mechanism	Sponsor	Status	Results	References (PMID)	Clinicaltrials.gov identifier
Ubiquinone and anti-oxidants	PO	Anti-oxidant	Univ. of Guadalajara	Phase II completed 2014	No		NCT02062034
Folic acid, B6, B12	PO	Anti-oxidant	Univ. of Catania	Phase IV completed 2014	No		NCT01921192
Sirolimus	Subconj.	Reduces IL-2 production	Santen	Phase I 2008; II 2012	No		NCT00401115
Pemafibrate	PO	PPARalpha agonist; anti-TG	Jaeb Center for Health Research	Phase III underway 2018	No		NCT03345901
Ruboxistaurin	PO	PKC-beta inhibitor	Chromaderm, Inc.	Phase III completed 2008;2010	Yes	23404115	NCT00266695
Ocustem	PO	"Increase circulation"	Aidan Products	Open label completed 2016	No		NCT02353923
Aminoguanidine	PO	Increase circulation	Univ. of Minnesota	Open label completed 2018	No		NCT02099981
Sirolimus	Subconj.	Anti-IL-2	NEI	Phase I/II completed 2012	Yes	21567211	NCT00711490
Keluo Xin	PO	Chinese Traditional Medicine	Chengdu University	Phase II underway 2017	No		NCT03258242
Squalamine	Topical	Anti-angiogenic	Elman Retina Group	Phase II completed 2014	No		NCT02349516
OC-10X	Topical	Tubulin inhibitor (anti-angiogenic)	OcuCure Therapeutics	Phase I completed 2013	No		NCT01869933
Candesartan	PO	ARB	AstraZeneca	Phase III completed 2008	Yes		NCT00252694
Fenofibrate	PO	PPARalpha agonist; anti-TG	Univ. of Padova	Phase IV completed 2015	No		NCT01927315
FOV2304	Topical	Kinin B1 receptor antagonist (anti-angiogenic)	Fovea Pharmaceuticals	Phase II completed 2012	No	Pruneau IOVS 2010	NCT01319487
TG100801	Topical	Anti-angiogenic	TargeGen	Phase I completed 2007	No		NCT00414999
Empagliflozin, glimepiride	PO	SGLT2 inhibitor versus sulfonylurea	Hannover Medical School	Phase IV underway since 2017	No		NCT02985242

Table 1 (*continued*)

Table 1 (*continued*)

Study agent	Route	Mechanism	Sponsor	Status	Results	References (PMID)	Clinicaltrials.gov identifier
THR-317	IVT	Anti-PIGF mAb	ThromboGenics	Phase II underway since 2016	No		NCT03071068
PF-04523655 (+/– ranibizumab)	IVT	siRNA against RTP801 (anti-angiogenic)	Quark Pharmaceuticals	Phase I/II completed 2013	No		NCT00701181
Sorbinil	PO	Aldose Reductase inhibitor	NEI	Phase III completed 2005	No		NCT00701181
Infliximab	IVT	Anti-TNFa	Retina Research Foundation	Phase I completed 2008	No		NCT00695682
Alpha lipoic acid	PO	Anti-oxidant	Ludwig-Maximilians University of Munich	Phase III completed 2005	No		NCT01208948
Darapladib	PO	Lp-Phospholipase A2 inhibitor	GlaxoSmithKline	Phase II completed 2013	No		NCT01506895
CD34+ stem cells	IVT	Unknown	Univ. of Calif., Davis	Phase I completed 2017	No		NCT01736059
iCo-007	IVT	anti-sense c-RAF kinase	iCo Therapeutics	Phase I completed 2012	No		NCT00886808
Tang Wang	PO	Chinese Traditional Medicine	Guang'anmen Hospital	Phase I underway 2017	No		NCT03025399
Fenofibrate	PO	PPARalpha agonist; anti-TG	Univ. of Sydney	Phase III completed 2013	No		NCT01320345

Table 2 Diabetic macular edema studies, Clinicaltrials.gov, December 2017

Study agent	Route	Mechanism	Sponsor	Status	Results	References (PMID)	Clinicaltrials.gov identifier
Teprotumumab	IV	IGF-1 receptor antagonist	River Vision development corporation	Phase I completed 2016			NCT02103283
Dextromethorphan	PO	NMDA receptor antagonism, insulinogenic	NEI	Open label, completed	Yes	25774850	NCT01441102
Opt-302 (and aflibercept)	IVT	VEGF-r/Fc-fusion	Opthea	Phase I/II underway 2017	No		NCT03397264
iCo-007	IVT	anti-sense c-RAF kinase	iCo	Phase I completed 2012	No		NCT00886808
Minocycline	PO	Anti-microglial	NEI	Phase II completed 2014	Yes		NCT01120899
SF0166	Topical	alphaVbeta3 integrin inhibitor	SciFluor	Phase I/II completed 2016	No		NCT02914613
RO6867461	IVT	bi-specific anti-VEGF/anti-angiopoietin 2	Hoffman-LaRoche	Phase II underway 2017	No		NCT02699450
REGN910-3 (nesvacumab)	IVT	anti-angiopoietin 2 mAb	Regeneron/Bayer	Phase II completed 2017	No	RUBY	NCT02712008
KH902 (Conbercept)	IVT	anti-VEGF receptor fusion protein	Chengdu Kanghong Biotech Co	Phase II completed 2013	No	28841827	NCT01324869
Danazol	PO	Decreased vessel permeability/angiogenesis	St. Michael's Hospital, Toronto, CA/Ampio Pharmaceuticals	Phase II/III completed 2013/6	No		NCT02002403
ALG-1001	IVT	Integrin receptor antagonist	Allegro Ophthalmics	Phase II underway 2017	No	LUMINATE	NCT02348918
Mecamylamine	Topical	NAchR antagonist	CoMentis	Phase II completed 2008	Yes	20189159	NCT00536692
Sirolimus	Subconj.	Reduces IL-2 production	Santen	Phase II completed 2012	No		NCT00656643
AKB-9778	Subcutaneous	Tie-2 activator +/– ranibizumab IVT	Aerpio Therapeutics	Phase II completed 2015	No	TIME-2; 27236272	NCT03197870
Bevasiranib, Cand5	IVT	SiRNA silencing of VEGF mRNA	Opko Health, Inc.	Phase II completed 2007	No		NCT00306904
AKB-9778	Subcutaneous	Tie-2 activator	Aerpio Therapeutics	Phase II completed 2014	No		NCT01702441
ASP8232	PO	AOC-3/VAP-1 inhibitor +/– ranibizumab	Astellas Pharma Europe B.V.	Phase II completed 2016	No		NCT02302079

Table 2 (*continued*)

Table 2 (*continued*)

Study agent	Route	Mechanism	Sponsor	Status	Results	References (PMID)	Clinicaltrials.gov identifier
KP-121	Topical	Lotemax suspension (corticosteroid)	Kala Pharmaceuticals	Phase II completed 2014	No		NCT02245516
Levosulpiride	PO	Dopamine receptor blocker, prolactinogenic	Universidad Nacional Autonoma de Mexico	Phase III underway 2016	No	16043870	NCT03161652
Choline fenofibrate	PO	Triglyceride reduction	Abbott	Phase II completed 2011	No		NCT00683176
MTP-131	Topical	Targets cardiolipin; increases mitochondrial ATP	Stealth Biotherapeutics	Phase I/II completed 2015	No		NCT02314299
KH-902 (Conbercept)	Intravitreal	anti-VEGF receptor fusion protein	Chengdu Kanghong Biotech Co	Phase III completed 2017	No	28841827	NCT01324869
Fasudil (and bevacizumab)	Intravitreal	Rho-kinase inhibitor; anti-proliferative	Shahid Beheshti University of Medical Sciences	Phase II completed 2015	No		NCT01823081
KVD001	Intravitreal	Plasma kallikrein inhibitor	Kalvista Pharmaceuticals	Phase I completed 2015	No		NCT02193113
Bromocriptine, Metoprolol, Tamsulosin	PO	Dopaminergic; anti-adrenergic	USC	Phase I/II not yet recruiting	No		NCT03384524
Tocilizumab (+/– ranibizumab)	IVT	Anti-IL-6	University of Nebraska	Phase I/II not yet recruiting	No		NCT02511067
Diclofenac	IVT	NSAID	Shahid Beheshti University of Medical Sciences	Phase I not yet recruiting	No		NCT00999791
PF-04523655 (+/– ranibizumab)	IVT	siRNA against RTP801 (anti-angiogenic)	Quark Pharmaceuticals	Phase I/II completed 2013	No		NCT00446381
REGN910-3 and 910 (+/– aflibercept)	IVT	anti-angiopoietin 2 mAb	Regeneron	Phase I completed 2015	No		NCT01997164
DS-7080a (+/– ranibizumab)	IVT	anti-angiogenic mAb	Daiichi Sankyo, Inc.	Phase I/II underway 2015	No		NCT02530918
FOV2304	Topical	Kinin B1 receptor antagonist (anti-angiogenic)	Fovea Pharmaceuticals	Phase II completed 2012	No	Pruneau IOVS 2010	NCT01319487
Darapladib	PO	Lp-Phospholipase A2 inhibitor	GlaxoSmithKline	Phase II completed 2013	No		NCT01506895

Table 2 (*continued*)

Table 2 (*continued*)

Study agent	Route	Mechanism	Sponsor	Status	Results	References (PMID)	Clinicaltrials.gov identifier
Nutritional supplements	PO	Anti-oxidative stress	Mid-Atlantic Retinal Consultations	Phase II completed 2011	No		NCT00893724
Ruboxistaurin	PO	PKC-beta inhibitor	Chromaderm, Inc.	Phase III completed 2011	Yes	23404115	NCT00133952
Sirolimus	Subconj.	Anti-IL-2	NEI	Phase I/II completed 2012	Yes	21567211	NCT00711490
THR-317	IVT	Anti-PIGF mAb	ThromboGenics	Phase II underway 2016	No		NCT03071068
BI 1026706	PO	Not publicly available	Boehringer Ingelheim	Phase II completed 2017	No		NCT02732951
LKA651	Intravitreal	Anti-erythropoietin	Novartis	Phase I underway since 2016	No		NCT02867735
Empagliflozin, glimepiride	PO	SGLT2 inhibitor versus sulfonylurea	Hannover Medical School	Phase IV underway since 2017	No		NCT02985242
Infliximab	IVT	Anti-TNF alpha mAb	Retina Research Foundation	Phase I completed 2008	Yes		NCT00695682
Alpha lipoic acid	PO	Anti-oxidant	Ludwig-Maximilians University of Munich	Phase III completed 2005	No		NCT01208948
Abicipar pegol	IVT	DARPin; anti-VEGF	Allergan	Phase II completed 2015	No		NCT02186119
BI 1467335	PO	Inhibitor of AOC3/SSAO/VAP-1; anti-inflammatory	Boehringer Ingelheim	Phase II underway 2017	No		NCT03238963

order to limit the discussion to novel therapies, we excluded those studies using established, conventional pharmacologic agents already in routine clinical use, specifically anti-VEGF agents (e.g., bevacizumab, ranibizumab and aflibercept) and corticosteroids (e.g., fluocinolone and dexamethasone). We also excluded all studies involving non-pharmacologic interventions, such as lasers and surgery, as well as all studies that were terminated, withdrawn, or suspended. This resulted in 43 and 45 studies, respectively, with an overlap of twelve studies between the two search terms (*Tables 1,2*). Many of the remaining clinical trials can be separated into one of several groups, including non-angiogenic targets, novel angiogenic factors, as well as new anti-VEGF agents. Given the relative paucity of published, peer-reviewed reports regarding many of the studies, we will focus the discussion to studies that appear to be active and may ultimately lead to broader commercial availability, as determined by press releases, recent presentations at conferences, or other publicly available information.

Integrin receptor antagonists

Novel therapeutic targets include anti-integrin therapy as exemplified by the peptide LUMINATE (ALG-1001, Allegro Therapeutics, San Juan Capistrano, CA, USA), which inhibits retinal neovascularization via interfering with integrin receptors essential for development of aberrant blood vessel growth (42). ALG-1001 is delivered by intravitreal injection, and has shown promising results with monthly administration either as a monotherapy or in combination with bevacizumab (43). As shown in *Table 2*, a phase II study is underway to determine the optimal therapeutic dose.

Angiopoietin-2/Tie2 pathway

The angiopoietin-2 (Ang2)/Tie2 tyrosine kinase pathway represents an attractive therapeutic target in DR and DME, given the data supporting a role for these proteins in contributing to the control of vascular permeability (44). AKB-9778 (Aerpio Therapeutics, Blue Ash, OH), is a small molecule inhibitor of VE-PTP, a critical negative regulator of Ang2/Tie2. It has the novelty of being a patient self-administered subcutaneous injection (similar to insulin) that has shown efficacy in promoting responsiveness to anti-VEGF therapy (ranibizumab) in DME or as a monotherapy (Time-2; *Tables 1,2*). REGN910-3 (nesvacumab) is a monoclonal antibody targeting Ang2 that was investigated conjointly by Regeneron and Bayer AG (Leverkusen, GER) in combination with aflibercept; per the latest press release in November 2017, it will not be pursued in a Phase III study. RG7716 is an agent by Hoffmann-La Roche AG (Basel, SUI) that is a bi-specific monoclonal antibody targeting VEGF and Ang-2. A phase II study has been completed with top line results showing statistically significant improvements of visual acuity at 6 months in patients with DR and DME treated with RG7716 versus ranibizumab (45). A phase III study is currently being discussed with the FDA.

Plasma kallikrein inhibitor

The kallikrein-kinin system represents a therapeutic target in DME independent of VEGF due to its effect on promoting vascular permeability (46).

KVD001 is an intravitreal administered plasma kallikrein inhibitor produced by Kalvista Pharmaceuticals (Cambridge, MA, USA) that completed a Phase I study in 2015 with promising results. Per the company website, a Phase II trial was announced in January of 2018 in collaboration with Merck (Kenilworth, NJ, USA), and oral plasma kallikrein antagonists are under development (47).

DARPin

Abicipar pegol is a DARPin (designed ankyrin repeat protein), a novel agent developed by Molecular Partners AG (Zurich-Schlieren, SUI) and investigated with Allergan that targets VEGF. DARPins are small, stable, high potency proteins and this particular molecule offers the advantage of longer duration of action and has yielded encouraging results in a phase II study completed in 2016; per the company website, it was equally efficacious as Lucentis in treating DME while being administered every 8 weeks (48). The timing of a Phase III trial remains unannounced at this time. They also describe a combination anti-VEGF/PDGF DARPin under development.

Conclusions

Treatments for DME and DR have undergone an evolution from initial laser based treatments to a variety of pharmacotherapies. While anti-VEGF agents and steroids remain the mainstay of pharmacotherapy for DR, many promising therapies are currently in the clinical pipeline.

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Footnote

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